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ORIGINAL ARTICLE

An exploratory analysis of alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223

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Background: Baseline clinical variables are prognostic for overall survival (OS) in patients with castration-resistant prostate cancer (CRPC). Their prognostic and predictive value with agents targeting bone metastases, such as radium-223, is not established.

Patients and methods: The radium-223 ALSYMPCA trial enrolled patients with CRPC and symptomatic bone metastases. Prognostic potential of baseline variables was assessed using Cox models. Percentage changes in biomarker levels from baseline were evaluated during the trial period; changes from baseline to week 12 were evaluated for association with OS and surrogacy.

Results: Eastern Cooperative Oncology Group performance status, total alkaline phosphatase (tALP), lactate dehydrogenase (LDH), and prostate-specific antigen (PSA) at baseline were associated with OS ($P \leq 0.0003$) in the intent-to-treat population (radium-223, $N = 614$; placebo, $N = 307$). tALP declined from baseline within 4 weeks after beginning radium-223, by week 12 declining in 87% of radium-223 and 23% of placebo patients ($P < 0.001$). LDH declined in 51% and 34% ($P = 0.003$), whereas PSA declined in 27% and 14% ($P = 0.160$). Mean tALP change from baseline was 32.2% decrease with radium-223 and 37.2% increase with placebo. Radium-223 patients with tALP decline from baseline to week 12 (confirmed $\geq$3 weeks from week 12) had 55% lower risk of death (hazard ratio = 0.45; 95% CI 0.34–0.61) versus those with no confirmed tALP decline. Proportional treatment effect (PTE) values for tALP, LDH, and PSA changes from baseline at week 12 as OS surrogate markers were 0.34 (95% CI: 0–0.746), 0.07 (95% CI: 0–0.211), and 0 (95% CI: 0–0.082), respectively.

Conclusions: Significant tALP declines (versus placebo) occurred as early as 4 weeks after beginning radium-223 therapy. tALP or LDH declines at 12 weeks correlated with longer OS, but did not meet statistical surrogacy requirements. Dynamic changes in tALP and LDH during radium-223 treatments may be useful to monitor, but do not serve as surrogates for survival.

Key words: radium-223, ALSYMPCA, CRPC, alkaline phosphatase, lactate dehydrogenase, prostate-specific antigen

Introduction

For individual patients with metastatic castration-resistant prostate cancer (mCRPC), prognostic models based on baseline clinical characteristics may be used to predict survival but are not currently used to monitor responses to therapy [1–5]. Serial bone scans [6] and advanced imaging methods [7] may serve this purpose, but simpler, less invasive, less expensive methods are needed to dynamically monitor therapy and inform decisions regarding treatment modification [8]. A surrogate marker that predicted overall survival (OS) in individual patients would be particularly useful in decisions regarding treatment modification [9].

Surrogacy requirements for OS in advanced prostate cancer were met for patients receiving docetaxel therapy by prostate-specific antigen (PSA) decreases ≥30% after 3 weeks of treatment in the SWOG 99-16 [10] and TAX327 [3] trials, and for patients receiving abiraterone acetate plus prednisone therapy or prednisone alone by the number of circulating tumor cells (CTC) and lactate dehydrogenase (LDH) levels after 12 weeks of treatment [11]. These surrogates may eventually aid in monitoring therapy with these agents, but further clinical investigation and validation are required [10, 12]. For ∼70% of advanced prostate cancer patients with bone metastases [8], bone-related markers (eg, total alkaline phosphatase [tALP]) are prognostic for OS [13–15] and tALP changes may be an early indicator of bone progression [8]. Both PSA and tALP changes are closely associated with survival, but PSA levels do not provide accurate information regarding extent of skeletal metastases or treatment effects on disease progression in bone. Therefore, tALP changes may correlate better with OS than PSA [16, 17].

The phase 3 ALSYMPCA trial established radium-223 efficacy and safety in CRPC patients with bone metastases [18, 19]. With radium-223, versus placebo, OS improved significantly (median 14.9 versus 11.3 months; hazard ratio [HR]=0.70; 95% confidence interval [CI]: 0.58, 0.83). Time to first symptomatic skeletal event was significantly prolonged (median 15.6 versus 9.8 months; HR = 0.66; 95% CI: 0.52–0.83), and secondary end points (including time to tALP increase, tALP response rate, and tALP normalization rate) favored radium-223 treatment [18, 19].

For mCRPC patients treated with radium-223, tALP changes properly established as a surrogate for survival could optimize treatment, allowing quick change of direction of therapies to patients most likely to benefit from such changes. Thus, exploratory analyses were conducted from ALSYMPCA to evaluate the treatment effect of radium-223 on changes in tALP, LDH, and PSA levels and assess their prognostic and predictive value.

Methods

ALSYMPCA compared efficacy and safety of radium-223 versus placebo, each plus best standard of care, in CRPC patients with symptomatic bone metastases [18]. Randomized patients (2:1) received six intravenous injections of radium-223 (50 kBq/kg IV [55 kBq/kg IV following US National Institutes of Standards and Technology update]) [20] or matching placebo, one injection every 4 weeks. The primary end point was OS.

Univariate and multivariate analyses with Cox proportional hazards models assessed the potential prognostic value for survival of selected baseline variables in placebo patients, radium-223 patients, and the intent-to-treat (ITT) population. Selected variables included prior docetaxel, prior hormone therapy, hemoglobin, serum albumin, tALP, PSA, LDH, Eastern Cooperative Oncology Group performance status (ECOG PS), opiate use, and age at study entry [4]. Kaplan–Meier analysis, after tertile grouping using baseline values, further illustrated the association of baseline tALP, PSA, and LDH with OS for radium-223 and placebo patients.

Changes from baseline in tALP, PSA, and LDH were assessed as least-squares mean percentage change at week 12, the halfway point of treatment, allowing consistency in protocol-defined timing of tALP and PSA measurements. Waterfall plots of maximum percentage change in tALP, LDH, and PSA from baseline to week 12 for each patient illustrated the magnitude of treatment effect. Dynamics of mean percentage change from baseline in biomarker levels, at each treatment visit and follow-up visits 12 and 24 weeks after last study-drug dose, were evaluated. OS by confirmed tALP or LDH decline at week 12 (decline confirmed ≥3 weeks from week 12) was evaluated. The relationship of relative risk of death to percentage changes from baseline at week 12 (last observation carried forward) was assessed using Cox proportional hazards modeling, including all baseline covariates.

Changes in tALP, PSA, and LDH from baseline to week 12 were evaluated as potential measures of OS surrogacy, as defined by Prentice [9], and quantified as a proportional treatment effect (PTE) [12]. PTE describes how much of the treatment effect on OS is explained by biomarker changes. PTE was calculated as 1 minus the ratio of (a) HR in the Cox proportional hazards regression model for survival with treatment (radium-223) plus the surrogate marker (tALP, PSA, LDH) to (b) that with treatment alone. Perfect surrogacy would be indicated by PTE = 1; no surrogacy, by PTE = 0. CIs were calculated according to Lin et al. [12], with a strong degree of surrogacy suggested if the 95% CI lower bound exceeded 0.5.

Results

Baseline prognostic factors

Multivariate analysis of baseline prognostic values as continuous variables was performed for placebo and radium-223 patients separately and for the entire ITT population (Table 1). For radium-223 patients, poor baseline ECOG PS and elevated baseline values for LDH, tALP, and PSA were associated with highest risk of death; for placebo patients, elevated baseline values for LDH and tALP were significantly associated with an increased risk of death. For the overall ITT population, opiate use was an additional significant baseline prognostic variable for OS. Kaplan–Meier analysis showed longer median survival among radium-223 patients in the lowest tALP tertile (≤131 U/L), versus those in the highest tertile (≥334 U/L) (23.9 versus 10.2 months); no overlap in the 95% CIs indicated a consistent trend across subgroups (supplementary Figure S1A, available at *Annals of Oncology* online). Placebo patients in the lowest (≤153 U/L) versus highest (≥360 U/L) tALP tertile also survived longer (median 18.8 versus 7.5 months) (supplementary Figure S1B, available at *Annals of Oncology* online). Similarly, longer survival was seen for radium-223 and placebo patients with lower versus higher baseline LDH (supplementary Figure S1C and D, available at *Annals of Oncology* online, respectively) and PSA values (data not shown).

Post-treatment changes from baseline

Changes from baseline were assessed at week 12 for tALP, LDH, and PSA for patients with baseline and week 12 determinations (sup

Table 1. Multivariate analysis of the correlation of baseline covariates with overall survival[a]

Baseline variable	HR[b]	*P* value[c]
Placebo patients		
Albumin	0.970	0.0652
ECOG PS (≥2 versus 0 or 1)	1.441	0.0839
Log LDH[d]	2.632	0.0043
Log tALP[d]	2.332	<0.0001
Log PSA[d]	1.250	0.0569
Age	1.009	0.3804
Radium-223 patients		
Albumin	0.972	0.0224
ECOG PS (≥2 versus 0 or 1)	1.775	0.0002
Log LDH[d]	4.244	<0.0001
Log tALP[d]	1.857	0.0001
Log PSA[d]	1.498	<0.0001
Age	1.018	0.0172
Overall ITT population		
Randomized treatment group	0.779	0.0074
Albumin	0.974	0.0069
ECOG PS (≥2 versus 0 or 1)	1.576	0.0003
Log LDH[d]	3.407	<0.0001
Log tALP[d]	2.017	<0.0001
Log PSA[d]	1.405	<0.0001
Age	1.016	0.0080
Opiate use (yes or no)	1.214	0.0379

[a]Baseline factors significantly associated with survival by univariate analysis were included in the multivariate analysis.
[b]HRs are relative risk for a 1-unit increase in the baseline variable for those without log transformation, or a 10-fold increase for those with log transformation.
[c]Based on Cox proportional hazards model.
[d]Log transformation was performed for baseline variables with heavily skewed distributions.
ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; ITT, intent-to-treat; PSA, prostate-specific antigen; tALP, total alkaline phosphatase.

plementary Figure S2, available at *Annals of Oncology* online). tALP decreased from baseline in 87% (433/497) of radium-223 patients versus 23% (49/211) of placebo patients ($P < 0.001$). For LDH, 51% (242/473) radium-223 and 34% (70/206) placebo patients showed a decrease ($P = 0.003$). PSA declined in 27% (135/493) of radium-223 and 14% (30/210) of placebo patients ($P = 0.160$) (supplementary Table S1, available at *Annals of Oncology* online). Waterfall plots, showing maximum percentage change in tALP and LDH at any time from baseline to week 12 for each patient in radium-223 and placebo groups, illustrated the between-group magnitude of difference in tALP response (supplementary Figure S3A, available at *Annals of Oncology* online) and a similarity in LDH response (supplementary Figure S3B, available at *Annals of Oncology* online), revealing a stronger association of tALP versus LDH declines with radium-223 treatment. No apparent difference was seen in waterfall plots of PSA response for radium-223 versus placebo (not shown).

Mean percentage change from baseline in tALP and LDH for radium-223 and placebo patients through 24 weeks of radium-223 treatment and follow-up are shown in Figure 1A and B. With radium-223, tALP decreases occurred as early as 4 weeks after treatment initiation, remained consistently low until treatment completion at 24 weeks, and remained significantly lower versus placebo patients at all time points to 46 weeks ($P < 0.001$) (Figure 1A). With placebo, tALP increased continuously through treatment and post-treatment follow-up. LDH levels for radium-223 patients were significantly lower versus placebo patients throughout most of the 24-week treatment period, but remained above baseline and increased through post-treatment follow-up at a rate similar to the placebo group rate (Figure 1B).

Relationship of post-treatment changes to OS and surrogacy

In an exploratory analysis, radium-223 patients with confirmed tALP or LDH decline from baseline at week 12 survived longer than those with no confirmed decline (Figure 2A and B). Among 497 patients with tALP values determined at baseline and week 12, 400 patients with a confirmed tALP decline had a median survival of 17.8 months and 55% lower risk of death (HR = 0.45; 95% CI: 0.34–0.61; $P < 0.0001$) versus 97 patients with no confirmed tALP decline (median survival, 10.4 months) (Figure 2A). Baseline characteristics were similar between patients with and those without confirmed decline. Although heavily weighted at the lower end by number of patients experiencing a tALP decrease, Cox regression modeling shows a near-linear relationship between percentage change in tALP from baseline (increase or decrease) at week 12 and risk of death, relative to no change in tALP (Figure 3A). Similarly, 196 radium-223 patients with an LDH decline from baseline to week 12 survived a median of 19.5 months and had a 45% lower risk of death (HR = 0.55; 95% CI: 0.42–0.73; $P < 0.0001$) versus 277 patients with no LDH decline (median survival, 14.5 months) (Figure 2B). Greater LDH increases, however, were associated with exponentially rapid increase in risk of death. Patients with a 300–400% increase in LDH at week 12 had an ∼7- to 14-fold greater risk than those with no LDH change (Figure 3B). In contrast, among 493 radium-223 patients with PSA values determined at baseline and week 12, PSA increased in 358 (73%) patients, often by factors of 10-fold or more. Multivariate analysis of the correlation between OS and PSA changes at week 12 showed that the impact of PSA changes at week 12 on risk of death was negligible (Figure 3C).

PTE values based on Cox regression models for tALP, LDH, and PSA changes from baseline at week 12 as surrogate markers of survival were 0.34 (95% CI: 0–0.746), 0.07 (95% CI: 0–0.211), and 0 (95% CI: 0–0.082), respectively. tALP had the highest PTE, but only modest surrogacy; a PTE = 0.34 indicates that the tALP decrease accounted for ∼34% of the survival benefit from radium-223 treatment.

Discussion

Multivariate analysis showed that elevated baseline tALP and LDH levels were associated with higher risk of death, compared with other factors, in placebo patients who did not receive

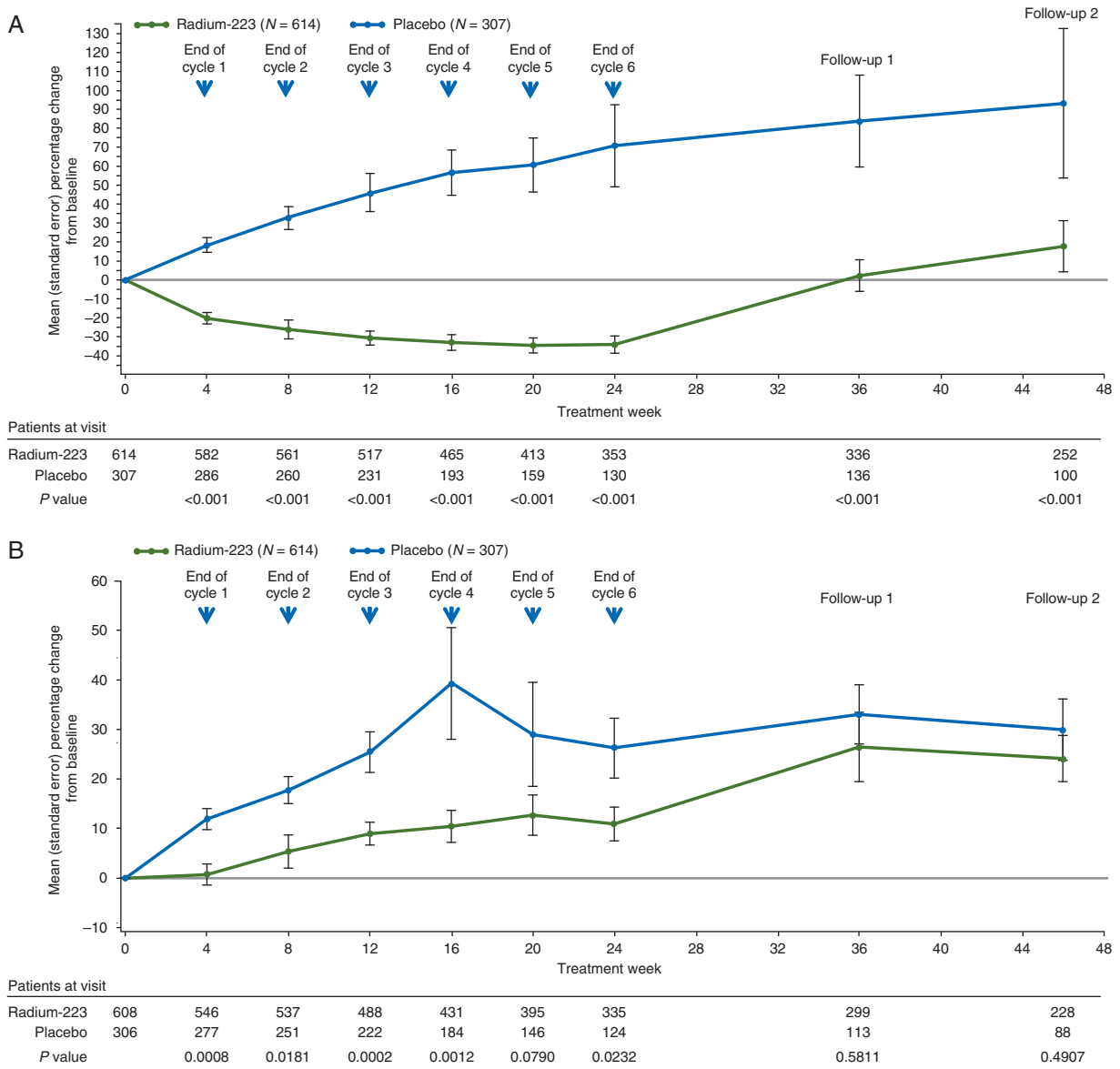

Figure 1. tALP and LDH dynamics in the ITT population. Mean percentage change in (A) baseline tALP and (B) baseline LDH at the end of each treatment cycle (6 cycles) and two follow-up visits. Six patients in the radium-223 arm and 1 in the placebo arm did not have baseline LDH determinations and were excluded from this analysis. ITT, intent to treat; LDH, lactate dehydrogenase; tALP, total alkaline phosphatase.

radium-223 treatment, as well as in radium-223-treated patients and the entire ITT population. Our findings for mCRPC patients with bone-only disease are consistent with similar studies in less defined populations and highlight the relative importance of tALP in this setting [2–5].

In ALSYMPCA, radium-223 treatment prolonged survival for patients with CRPC and bone-only metastases [18]. In this *post hoc* analysis, we report confirmed tALP declines in 80% of evaluable patients after 12 weeks of receiving radium-223 and their association with decreased risk of death, suggesting that changes in tALP could potentially be a surrogate for survival useful in managing patients receiving radium-223 therapy. The ALSYMPCA findings meet the requirements for a surrogacy analysis as described by Prentice [9]. PTE surrogacy analysis showed tALP decreases at 12 weeks from baseline to be a moderate predictor of survival, with PTE = 0.34 and a broad CI (0.0, 0.746). The analysis also indicated that radium-223 effects on LDH or PSA contributed little or nothing to the radium-223-associated survival benefit. Our tALP findings were consistent with those reported in TAX327, which showed an association with OS but could not establish surrogacy for tALP changes in patients with bone metastases [16].

Responses to chemotherapy are likely related to a combination of factors: the patient's underlying physical condition and probably other factors reflected or not in biomarker levels, such as pain score and visceral organ involvement. Scher and colleagues [11], in their phase 3 study of abiraterone acetate–prednisone, reported a high level of surrogacy for a biomarker panel consisting of the combination of circulating tumor cell (CTC) count and LDH level at 12 weeks. They used Prentice criteria [9] to establish relative surrogacy, but did not assess PTE. The CTC-LDH combination was superior to CTC or LDH alone or to CTC

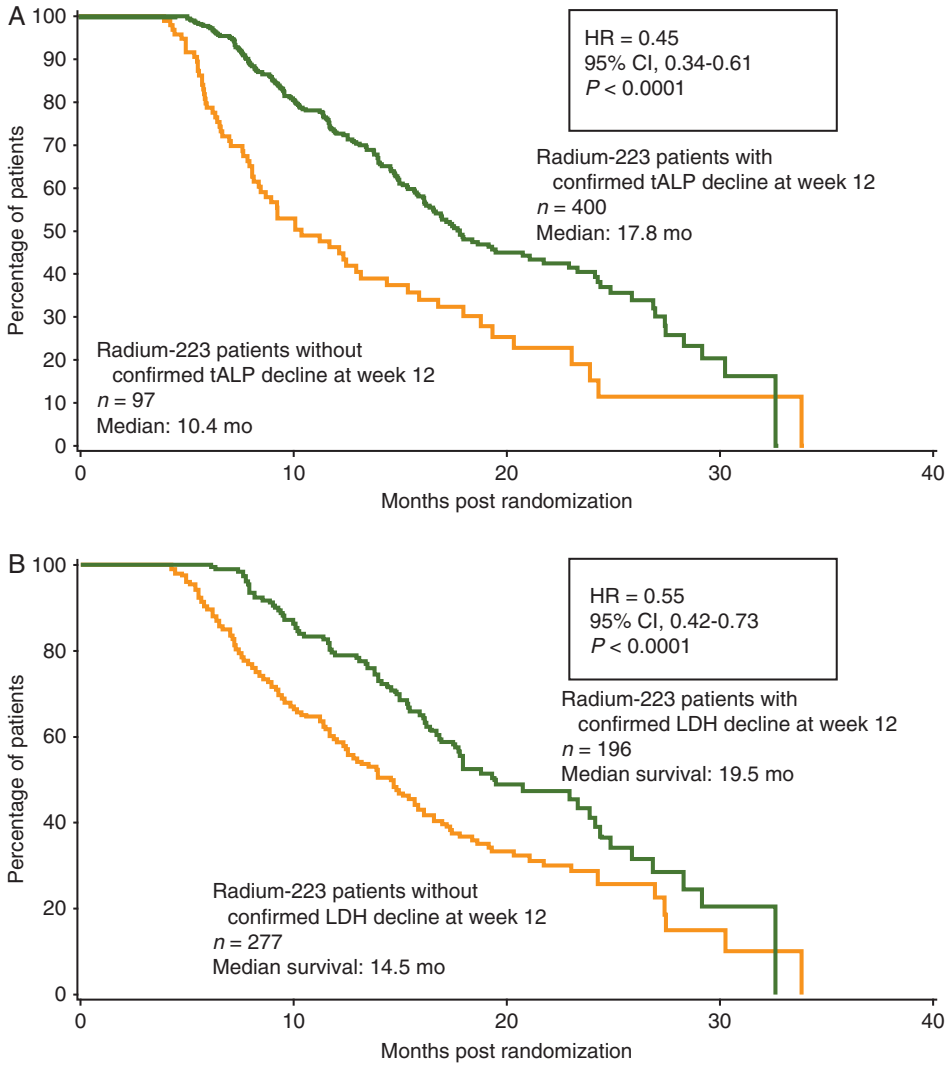

Figure 2. Overall survival in the radium-223 cohort with and without a confirmed decline in (A) baseline tALP and (B) baseline LDH at week 12. Confirmed decline was defined as any decrease from baseline at week 12, confirmed ≥3 weeks later. LDH, lactate dehydrogenase; tALP, total alkaline phosphatase.

combination with any other biomarkers, including tALP decreases and ≥30% or ≥50% PSA decreases. Future assessments of the validity of markers in predicting effectiveness of chemotherapy may be more successful when combinations of factors are considered.

Limitations in our study influenced our conclusions: The exploratory analysis was not included in the original ALSYMPCA study plan; other relevant bone markers and markers such as CTCs, not prospectively determined in this phase 3 study, could not be considered. We analyzed only biomarker level decreases from baseline to 12 weeks. If we considered specific rates of decline, as in the PSA studies, we may have arrived at a higher PTE value, but the patient number in each group may have been inadequate for statistical analysis. We evaluated markers individually, not in combination; the proportion of patients showing LDH and PSA decreases did not appear to justify the more extensive analysis. Future prospective studies addressing these limitations may identify more promising candidates for surrogacy. With these caveats, we found that changes in tALP, LDH, and PSA levels after 12 weeks of treatment are not surrogates for survival for patients with CRPC and bone metastases treated with radium-223. The effective course of radium-223 treatment in ALSYMPCA was 24 weeks, with 6 cycles given at 4-week intervals. Using biomarker changes, particularly rising PSA levels, to make decisions about continuing radium-223 presents a substantial risk that a large fraction of patients who may benefit will be denied effective treatment. Monitoring biomarkers during treatment may have benefit as an indication for radiologic evaluation of disease status [8].

The observed tALP changes with treatment raise questions about radium-223 treatment duration and underline the need for a reliable marker of radium-223 efficacy. In ALSYMPCA with radium-223, the rapid and sustained tALP declines and the increasing tALP suppression with continued therapy reflected the radionuclide mechanism of action in the bone microenvironment, consistent with rapid and progressive inhibition of ALP production by osteoblasts. Dynamic profiles of both tALP and LDH levels during the study suggest that treatment durations

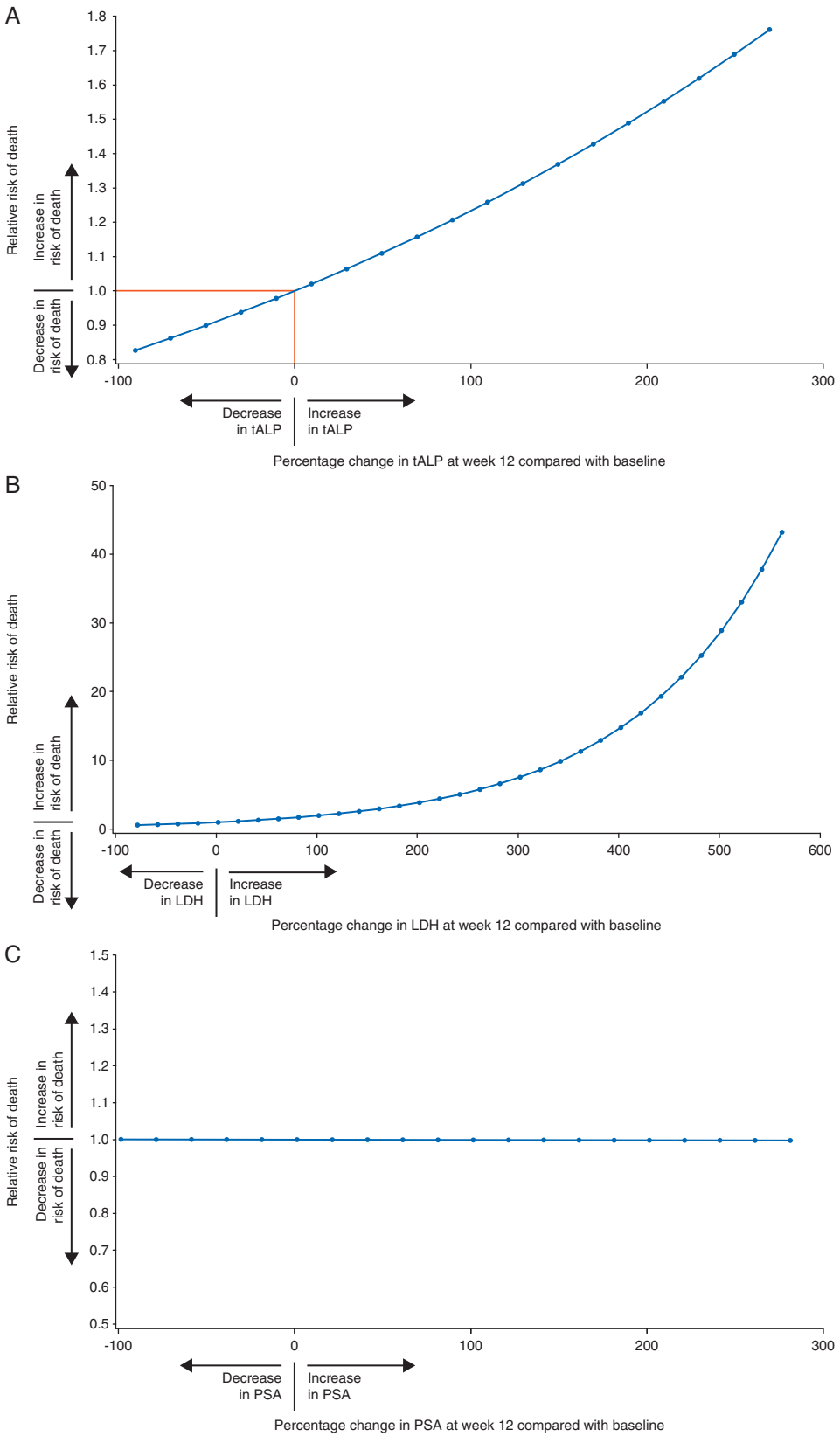

Figure 3. Relationship between percentage change in (A) tALP, (B) LDH, and (C) PSA levels from baseline and risk of death relative to no change in tALP, LDH, or PSA in the ITT population with baseline marker analyses. The red lines in (A) define the area of decreasing risk of death with decreases in tALP from their baseline level. To make (C) PSA comparable to (A) tALP, its x axis was truncated to include only patients with PSA percentage changes from baseline between -100% and 300%; 46 of 910 (5.1%) patients with percentage changes in PSA >300% were excluded. LDH, lactate dehydrogenase; PSA, prostate-specific antigen; tALP, total alkaline phosphatase.

>24 weeks should be tested. Although we could not determine whether tALP changes were a direct effect on cancer cells or on osteoblasts, preclinical studies suggest that tALP is a marker of pharmacodynamic effect and that radium-223 impacts both osteoblasts and tumor cells [21, 22]. In a human prostate cancer model, characterized by osteoblastic growth, PSA production, and systemic metastases when inoculated into the bone marrow cavity, radium-223 inhibited disease progression, reduced tumor volume, and decreased areas of tumor in tumor-bearing tibias. Tumor-induced osteoblastic bone growth was suppressed and normal architecture was maintained, leading to reduced bone volume in tumor-bearing bone. Radium-223 induced double-strand DNA breaks in tumor cells and osteoclasts, consistent with potent radiation effects of radium-223 in the tumor microenvironment [21, 22]. Such models in prostate cancer, and others in breast cancer [23], are important in addressing questions about radium-223 mode of action in cancer patients.

In conclusion, significant tALP declines (versus placebo) occurred as early as 4 weeks after initiation of radium-223 therapy. tALP or LDH decline at 12 weeks correlated with longer OS, but did not meet statistical surrogacy requirements. Changes in tALP and LDH are dynamic during radium-223 treatments and may be useful to monitor, but do not serve as surrogates for survival.

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Disclosure

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References

1. Smaletz O, Scher HI, Small EJ et al. Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. J Clin Oncol 2002; 20: 3972–3982.
2. Halabi S, Small EJ, Kantoff PW et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. J Clin Oncol 2003; 21: 1232–1237.
3. Armstrong AJ, Garrett-Mayer ES, Yang YC et al. A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. Clin Cancer Res 2007; 13: 6396–6403.
4. Halabi S, Lin CY, Small EJ et al. Prognostic model predicting metastatic castration-resistant prostate cancer survival in men treated with second-line chemotherapy. J Natl Cancer Inst 2013; 105: 1729–1737.
5. Halabi S, Lin CY, Kelly WK et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2014; 32: 671–677.
6. Imbriaco M, Larson SM, Yeung HW et al. A new parameter for measuring metastatic bone involvement by prostate cancer: the Bone Scan Index. Clin Cancer Res 1998; 4: 1765–1772.
7. May EJ, Viers LD, Viers BR et al. Prostate cancer post-treatment follow-up and recurrence evaluation. Abdom Radiol (NY) 2016; 41: 862–876.
8. Kamiya N, Suzuki H, Endo T et al. Clinical usefulness of bone markers in prostate cancer with bone metastasis. Int J Urol 2012; 19: 968–979.
9. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 1989; 8: 431–440.
10. Petrylak DP, Ankerst DP, Jiang CS et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. J Natl Cancer Inst 2006; 98: 516–521.
11. Scher HI, Heller G, Molina A et al. Circulating tumor cell biomarker panel as an individual-level surrogate for survival in metastatic castration-resistant prostate cancer. J Clin Oncol 2015; 33: 1348–1355.
12. Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Stat Med 1997; 16: 1515–1527.
13. Cook RJ, Coleman R, Brown J et al. Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. Clin Cancer Res 2006; 12: 3361–3367.
14. Fizazi K, Massard C, Smith M et al. Bone-related parameters are the main prognostic factors for overall survival in men with bone metastases from castration-resistant prostate cancer. Eur Urol 2015; 68: 42–50.
15. Chi KN, Kheoh T, Ryan CJ et al. A prognostic index model for predicting overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate after docetaxel. Ann Oncol 2016; 27: 454–460.
16. Sonpavde G, Pond GR, Berry WR et al. Serum alkaline phosphatase changes predict survival independent of PSA changes in men with castration-resistant prostate cancer and bone metastasis receiving chemotherapy. Urol Oncol 2012; 30: 607–613.
17. Parker CC, Pascoe S, Chodacki A et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in

patients with bone metastases and castration-resistant prostate cancer. Eur Urol 2013; 63: 189–197.
18. Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369: 213–223.
19. Sartor O, Coleman R, Nilsson S et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. Lancet Oncol 2014; 15: 738–746.
20. Zimmerman BE, Bergeron DE, Cessna JT et al. Revision of the NIST standard for ^{223}Ra: new measurements and review of 2008 data. J Res Natl Inst Stand Technol 2015; 120: 37–57.
21. Suominen MI, Fagerlund KM, Rissanen JP et al. Radium-223 dichloride—efficacy and mode-of-action in a mouse model of prostate cancer bone metastasis. Eur J Cancer 2014; 50: Abstract 63 [poster PO57].
22. Suominen MI, Fagerlund KM, Rissanen JP et al. Radium-223 dichloride exhibits dual mode-of-action inhibiting both tumor and tumor-induced bone growth in two osteoblastic prostate cancer models. Cancer Res 2015; 75 (15 suppl): Abstract 3447 [poster].
23. Suominen MI, Rissanen JP, Kakonen R et al. Survival benefit with radium-223 dichloride in a mouse model of breast cancer bone metastasis. J Natl Cancer Inst 2013; 105: 908–916.